LETTERS TO THE EDITOR

Modification of the Inflammatory Activity of Psoriatic Arthritis in Patients Treated with Extract of Polipodium leucotomos (Anapsos®)

SIR—Psoriatic arthropathy is a well-defined inflammatory joint disease that develops in ~5% of patients with psoriasis, with an estimated prevalence of ~0.1%. Twenty per cent of polyarticular patients develop progressive, destructive arthritis, and 10–20% advance toward mutilated joints [1]. The treatment used in psoriatic arthritis is similar to that used in other chronic inflammatory joint diseases, but several other treatments specific to skin diseases have improved the arthritis.

Anapsos, an extract from the rhizomes of the fern Polipodium leucotomos, native to Central America, has been shown to reduce the rate of incorporation of nucleoproteins and protein precursors, and to exert immunomodulatory effects [2, 3]. We have shown an increased production of IL-2, IL-10 and interferon-γ during in vitro studies on the human peripheral blood mononuclear cells (HPBMC) of healthy controls [4], and the drug is used for the treatment of atopic dermatitis and psoriasis. To study the effect on the activity of peripheral inflammatory psoriatic arthritis, we treated five females and eight males (mean age 43 yr) in an open, prospective trial.

Patients had swelling and stiffness in four or more peripheral joints. They also had chronic plaque-type skin lesions of psoriasis, with a negative rheumatoid factor. Exclusion criteria included other known systemic disorders or corticosteroid treatment. All patients gave informed consent after a full explanation of the details and procedures. Statistical analysis used a Wilcoxon test.

The 13 patients (seven oligoarthritics and six polyarthritics), with a mean arthropathy evolution of 7 ± 3 yr, were treated with 720 mg/day of Anapsos (Regender®), for a minimum of 6 months. All patients were examined in a special out-patient clinic at −1, 0, 3 and 6 months. Overall patient assessment was classified using a four-point scale.

Twelve patients were included in the final evaluation, because one withdrew. Although we observed a tendency for the HAQ to improve, differences were not significant (median 0.87; quart1: 0.425/quart3: 1.425 at entry vs 0.75; quart1: 0.4/quart3: 1.5 at 6 months). There was a reduction of the pain score (10 cm VAS) from 66.5 (quart1: 40; quart3: 71) to 49 (quart1: 34; quart3: 65.5) (P < 0.05). The number of inflamed joints [four (quart1: 3; quart3: 6.5) initial vs two (quart1: 1; quart3: 2.5) final (P < 0.01)] and CRP [21.75 (quart1: 5.1; quart3: 43) vs 13.7 (quart1: 6.3; quart3: 21.6)] were reduced significantly. A similar evolution was shown with the skin, with the final difference being significant (P < 0.01): 2.5 (quart1: 2; quart3: 3) vs 1 (quart1: 0.5; quart3: 1.5). The overall evaluation by patient shows an improvement; the initial value of two (quart1: 1.5; quart3: 3) was significant when compared to the final value of one (quart1: 1; quart3: 1) (P < 0.01). The ESR, Hb and lymphocyte subsets were unaltered, as were the IgM, IgA and IgG levels with differences not significant.

Our study showed an improvement of the arthritis and skin disease in a group of patients with severe psoriatic arthritis. We believe that these results, although obtained in an open trial, are sufficiently encouraging to warrant further studies of larger numbers in a controlled fashion.

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An Unusual Case of Carpal Tunnel Syndrome

SIR—A 54-yr-old woman on warfarin, following a prosthetic valve replacement, presented with an acutely

| TABLE I | Main parameters for 12 psoriatic arthritic patients who completed the trial with Anapsos® |
|---------|------------------------|--------|--------|
|         | Initial | 6 months | P    |
| HAQ*   | 0.87    | 0.75    | ns    |
|         | q: 0.425/1.425 | q: 0.4/1.5 |       |
| VAS (pain; mm) | 66.5 | 49 | <0.05 |
|         | q: 40/71 | q: 34/65.5 |       |
| No. of joints involved | 4 | 2 | <0.01 |
|         | q: 3/6.5 | q: 1/2.5 |       |
| Skin score | 2.5 | 1 | <0.01 |
|         | q: 2/3 | q: 0.5/1.5 |       |
| Overall evaluation | 2 | 1 | <0.01 |
|         | q: 1.5/3 | q: 1/1 |       |
| CRP    | 21.75   | 13.7    | <0.05 |
|         | q: 5.1/43 | q: 6.3/21.6 |       |
| ESR    | 40.5    | 28.5    | ns    |
|         | q: 28/51 | q: 18.5/50 |       |

Values (median, quart 1 and 3). Wilcoxon test.

*Modified for PA.
painful right hand as an emergency to the casualty department. The pain had started suddenly the previous evening, when she had attended for the first time. There was no prior trauma and no bruise was noted. No symptoms suggestive of nerve compression were reported initially. X-ray of the hand was normal and she was advised to take analgesics and discharged. She presented again the following morning because of worsening pain overnight and she was also starting to experience paraesthesiae in the median nerve distribution. A small defined area of bruising on the volar aspect of her right forearm at the wrist had also developed. On closer questioning, she recalled resting a half-full saucepan on her forearm the previous afternoon.

There was a past history of rheumatic fever as a child and in 1974 she underwent mitral and aortic valve replacements (Bjork Shiley) for which she was on long-term oral warfarin. Her INR (international normalized ratio) was monitored regularly at the anticoagulant clinic and control over the past 25 yr had been satisfactory.

Physical examination revealed a fluctuant swelling on the palmar aspect of her right wrist measuring ~2 × 1 cm and an overlying small bruise was visible. She had objective evidence of right median nerve compression. Apart from evidence of previous cardiac surgery, examination was unremarkable.

Investigations showed that the INR was initially raised at 4.9. Ultrasonography of the right wrist showed a hypoechoic area within the flexor sheath measuring 1 × 1 cm (Fig. 1). Aspiration with a 23-g needle under ultrasound guidance yielded 1.5 ml of blood. Nerve conduction studies 2 days later showed prolongation of the distal sensory latency and diminution of amplitude in the right median nerve. Needle EMG studies on the abductor pollicis brevis showed manifestations of acute denervation—confirmatory evidence of acute median neuropathy across the wrist.

Aspiration of the carpal tunnel gave her immediate, albeit partial, relief. Her warfarin dose was stabilized. At the time of her discharge, her pain had settled considerably, although there was persistent paraesthesiae. Surgical exploration was not considered appropriate as there was no demonstrable haematoma on a repeat ultrasound. She was advised to use a splint for her hand. Her symptoms resolved over the next 3 months. A repeat nerve conduction study 6 months later showed a marked improvement in both motor and sensory parameters of the right median nerve. Needle EMG indicated cessation of the acute denervation process and features of regeneration.

This case illustrates a rare but well-recognized cause of acute carpal tunnel syndrome [1–4]. Our patient was on long-term oral anticoagulation and this was poorly controlled at the time she presented with a haematoma within the flexor sheath at the wrist. It is very likely that the mild trauma of resting a saucepan on her wrist, combined with a high INR, contributed to the development of a haematoma.

Haemorrhagic complications related to long-term anticoagulation can be divided into minor or major ‘life-threatening’ complications. The reported incidence of major complications is between 4.4 and 8.2% [5]. The incidence of minor complications is less well documented, but ranges from entrapment neuropathies, compartment syndromes and minor bleeding from different sites, e.g. the nose, bowel and urinary tract. The duration of therapy appears to be an important factor and generally the longer the duration of therapy, the higher the chance of bleeding. Prolongation of the prothrombin time beyond the therapeutic range, as in our case, is another risk factor.

A very similar case reported earlier [1] had florid signs of swelling, tenderness and a flexion deformity of the fingers. She required surgical evacuation and her recovery was complicated by re-bleeding which necessitated further surgical exploration.

Most cases of acute carpal tunnel syndrome secondary to a coagulopathy occur in haemophiliacs [6, 7]. In one study [6], out of the five haemophilia patients with entrapment neuropathies, two made a complete recovery and three had a residual neurological deficit. In haemophiliacs and patients on oral anticoagulants, venepuncture and arterial puncture have been associated with the development of haematomas [8, 9].

Fortunately, our patient made a slow but almost complete recovery. Early recognition of the condition is important because, as demonstrated in this case, a delay of hours can lead to significant nerve damage. The choice of treatment depends on the extent of the haemorrhage. Early surgical intervention after correction of the coagulopathy is advocated for larger haematomas. In our case, needle aspiration was adequate in relieving symptoms. Serial ultrasound examination of the wrist was useful in monitoring progress.

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**Tumour Markers in Dermatomyositis: Useful or Useless?**

Sir—The association of dermatomyositis (DM) with malignancy has been recognized for many years, although the frequency of the association is debated to range from 15 to 50% [1, 2]. The value of tumour markers in the detection of cancer is controversial, and recent guidelines [3] suggest that they are not recommended as a screening test for many common tumours. However, there are a number of reports relating particular markers to tumours associated with DM [4–6].

We report the case of a 36-yr-old woman who first presented with classical DM in June 1996, with a facial macular rash, Gottron’s papules, a proximal myopathy, minimally elevated creatinine kinase (CK) at 234 IU/l (normal range 25–170), and typical features on both skin and muscle biopsies. She was a lifelong non-smoker. At presentation, a routine screen for malignancy was unremarkable, including normal chest X-ray and mammography.

She responded well to combination therapy with prednisolone and methotrexate. Seven months after the initial presentation, she had to increase both drugs because of a relapse of the facial rash. This initially resolved, but she relapsed 4 months later. During that time, the tumour marker carcinoembryonic antigen (CEA; associated primarily with colorectal carcinoma, but also elevated in tumours of lung, breast and pancreas) was being measured by her general practitioner (GP), unknown to the rheumatology service. A small elevation 6 months after presentation (8.8 mg/ml, normal <5) was significantly higher 5 months later (57 mg/ml). The trend was confirmed on a further sample 2 months later (167 mg/ml), at which time we were informed (in retrospect, rather too late). Subsequent re-assessment revealed right upper lobe bronchogenic carcinoma with mediastinal nodal involvement.

Those with DM difficult to keep in remission, such as our case, are thought to have a higher incidence of associated malignancy. In addition, a normal CK level (near normal in our patient) has been identified as a poor prognostic sign [7]. While there is broad consensus among oncologists that no tumour marker is sufficiently sensitive or specific for screening purposes, Bayes’s theorem demonstrates that in a population with a higher incidence (prior probability) of a disease (malignancy), the usefulness of a test increases (see nomogram in [8]). Our case highlights the identification of an asymptomatic lesion in a patient at risk, due to monitoring (some would say overenthusiastic!) by her GP. We suggest that tumour markers may be of value in detecting disease at an earlier, treatable stage in such patients, particularly should they relapse. Our case rests.

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**Serious Opportunistic Infection Associated with Gold-induced Panhypogammaglobulinaemia**

Sir—A 39-yr-old woman diagnosed as having seronegative rheumatoid arthritis in 1995 was initially treated with prednisolone 10 mg daily and sulphasalazine 2 g daily. A satisfactory initial clinical response was not maintained and, after 9 months, treatment with i.m. gold (myocrisin) was commenced. After a total dose of 600 mg of gold, at a time when joint symptoms were improving, she developed multiple painful pustules on the fingers and forearms which responded to oral fluocoxacin 500 mg q.d.s. One week later, she complained of severe breathlessness, right-sided pleuritic chest pain and rigor, and was admitted as an emergency. On examination, she was pyrexial (39°C), tachycardic and cyanosed with fine, late inspiratory crackles audible in both lung fields.

Initial investigations were as follows: haemoglobin...
13.6 g/dl, white cell count 9.1 × 10⁹/l, platelets 294 × 10⁹/l, blood gases on air pH 7.51, pO₂ 6.52 kPa, pCO₂ 2.9 kPa, HCO₃ 25.1. The C-reactive protein (CRP) was 64 mg/l. Urea, creatinine, electrolytes and liver function tests were normal. Chest radiograph, which had been normal 1 month earlier, now showed diffusely increased interstitial lung markings, but no focal consolidation. Although the CD4⁺ T-lymphocyte count was normal, the clinical and radiological features were suggestive of Pneumocystis carinii pneumonia and treatment with high-dose i.v. cotrimoxazole (120 mg/kg/day) and oxygen was therefore commenced. Subsequent bronchoalveolar lavage failed to confirm the diagnosis, but the patient improved, and the symptoms and signs resolved over the next 7 days. The blood gases and CRP normalized over a 3 week period.

Further investigations revealed that the patient was panhypogammaglobulinaemic: IgG 1.39 g/l (5.1–15.8 g/l), IgA 0.1 g/l (0.8–4 g/l), IgM 0.2 g/l (0.48–1.9 g/l). Immunoglobulin levels had been normal prior to starting gold treatment (IgG 8.93 g/l, IgA 1.3 g/l, IgM 1.4 g/l). A diagnosis of myocrisin-induced panhypogammaglobulinaemia was made and therapy was stopped. Replacement therapy with i.v. gammaglobulin (Vigam5) was started and plans made for therapy to be administered every 2 weeks. However, during the next 6 weeks, the IgA and IgM levels increased and returned to the normal range. Because this process reflected recovery of endogenous immunoglobulin production (immunoglobulin preparations for replacement therapy consist almost entirely of IgG), no further i.v. immunoglobulin infusions were given. IgG levels continued to increase and 6 months after admission were within the normal range, and the patient was well. Changes in the immunoglobulin levels in relation to gold therapy are illustrated graphically in Fig. 1.

Mild suppression of serum immunoglobulin levels occurs in ~50% of patients treated for rheumatoid arthritis with parenteral gold salts [1] and, providing there are no infective complications, treatment can be continued [2]. Severe panhypogammaglobulinaemia resulting in infections is rare [2–4]. The largest survey of gold-induced hypogammaglobulinaemia describes 22 patients collected from a single unit over a 10 yr period [2]. Nineteen patients had deficiencies of one or two immunoglobulin isotypes, but only three patients had panhypogammaglobulinaemia. Recurrent chest infections were observed in four subjects, but the causative organisms were not reported. There was no relationship between the duration of treatment, total dose of gold given and the occurrence of immunoglobulin deficiency. One patient remained panhypogammaglobulinaemic after 4 yr, but immunoglobulin levels returned to normal in the other cases within 18 months. The authors estimated that 2% of patients treated with gold may develop immunoglobulin deficiency, and recommended that measurement of immunoglobulin levels should be undertaken in all patients before and during treatment with gold.

Gold-induced panhypogammaglobulinaemia resulted in severe, life-threatening, opportunistic pulmonary infection in our patient. The extent of the immunoglobulin deficiency which can occur during the course of gold therapy is very variable and, although panhypogammaglobulinaemia is rare, its association with potentially serious bacterial infection is clinically important. Although reversible in many instances, immunoglobulin replacement therapy may be temporarily indicated. Permanent panhypogammaglobulinaemia requires life-long immunoglobulin replacement therapy.

Defects in immunoglobulin production have also been described in association with other disease-modifying anti-rheumatic drugs (DMARDs) [5], such as penicillamine [2], sulphasalazine [6] and methotrexate [2]. Although an asymptomatic, mild deficiency of a single immunoglobulin isotype is the most common abnormality, panhypogammaglobulinaemia has been reported for each of these agents and may occur in up to 1% of patients on sulphasalazine [6].

The case we have described highlights the importance of considering hypogammaglobulinaemia in patients who develop infections whilst receiving gold treatment, a complication which is not mentioned in the guidelines on the monitoring of second-line drug treatment published by the British Society for Rheumatology [7] or the manufacturer’s product data sheets [8]. Early detection and withdrawal of the drug may favour recovery of endogenous immunoglobulin production.

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Necrotizing Arteritis Confined to Striated Muscle Mimicking a Soft-tissue Tumour in a Patient with Rheumatoid Arthritis

Sir—Patients with RA occasionally develop a necrotizing arteritis that shares most of the clinical and pathological features of isolated polyarteritis nodosa (PAN). A very unusual form of PAN is characterized by the limited involvement of only striated muscle with focal areas of myositis and necrotizing vasculitis. We report herein what is, to the best of our knowledge, the first case reported in the English medical literature of this limited form of necrotizing arteritis associated with RA.

A 43-yr-old White woman with a 10 yr history of RF-positive, erosive RA complained, during a routine check-up to monitor her disease, of the gradual onset of a painless mass in her left thigh. The patient presented no joint symptoms. She was being treated with prednisone (5 mg/day). There was no fever, weight loss, asthenia or previous trauma. On examination, a firm mass measuring 4 × 2 cm was noted in the lateral aspect of her left thigh. The mass was not tender or attached to deep tissues or skin. The skin was not warm or erythematous. The patient was afebrile. There was no joint swelling and general exam revealed no abnormalities. With the presumptive diagnosis of a soft-tissue tumour of recent onset, a plain radiograph and MRI were ordered. The X-ray film revealed a soft-tissue swelling and normal adjacent femur without periostitis. MRI showed a 9 × 1 cm mass in the left vastus lateralis, isointense with the muscle in T1-weighted sequences, and a bright signal in T2-weighted and STIR sequences. A biopsy was performed without removal of the mass. The pathological study showed atrophy of the muscle fibres and an intense inflammatory infiltrate composed mainly of lymphocytes. The medium-sized arteries showed an inflammatory infiltrate in vessel walls with fibrinoid necrosis (Fig. 1). With the diagnosis of necrotizing arteritis involving striated muscle, the patient was re-evaluated. There was no sign of systemic hyper-tension, fever, weakness, paraesthesiae, rash or any systemic complaint. The patient remained afebrile and felt well. A new physical exam was normal. Blood cell count, ESR, liver enzymes, plasma creatinine concentration and creatinine clearance were within normal limits. Creatine phosphokinase, aldolase and electromyography were normal. The arteriography of mesenteric, hepatic and renal arteries disclosed no abnormality. Since there was no evidence of systemic involvement and the mass was growing smaller spontaneously, we decided to wait and see. Six months later, the mass was not detected on physical examination and a new MRI showed only a linear signal in the vastus lateralis muscle with a bright signal on T2-weighted images. After a follow-up of 24 months, there has been no new flare of localized necrotizing arteritis.

The patient described herein had RA associated with necrotizing arteritis circumscribed to her left thigh that clinically mimicked a soft-tissue tumour. There was no clinical evidence of systemic disease and all other tests were normal or negative. The disease evolved towards a spontaneous recovery without therapy. We actively ruled out visceral involvement by a clinical and analytical evaluation, muscle enzymes, arteriography and electromyography. PAN is very rarely identified as the cause of focal enlargement of striated muscle. Our literature review disclosed six cases of localized PAN involving lower extremity muscles. Golding [1] described a 40-yr-old man whose disease was limited to the calves, without involvement of adjacent skin. Leib et al. [2], in their series of 64 patients with PAN, found only two patients with localized vasculitis of the muscle with calf pain and swelling. Laitinen et al. [3] described a 33-yr-old woman with a 14 yr history of undifferentiated connective tissue disease who developed fever, skin eruption on her legs, a high ESR, and ankle muscle swelling and tenderness. Biopsy of the calf muscles revealed necrotizing arteritis. Ferreiro et al. [4] described a 47-yr-old man with fever of undetermined origin and bilateral calf swelling. Biopsy of calf muscle showed necrotizing arteritis and features.
of myositis. Esteva-Lorenzo et al. [5] described a 56-yr-old man with a 7 yr history of pain and swelling in his right thigh, periosteaal new bone formation and increased T2 signal on MRI of right quadriceps and biceps femoris. A biopsy of the vastus medialis muscle revealed fibrinoid necrosis of medium and small-sized arteries.

Necrotizing arteritis circumscribed to striated muscle is a rare disease that can appear in association with other autoimmune diseases such as RA (present case) or undifferentiated connective tissue disease [3]. The muscle groups most frequently affected are the calves, usually bilaterally. The patient complains of pain, diffuse swelling and stiffness, although on rare occasions the disease presents as a soft-tissue mass, as in our case and that of Esteva-Lorenzo [5]. The course of the disease can be acute, subacute or relapsing, with flares and asymptomatic periods. Frequently, there is evidence of systemic inflammatory activity with fever [3, 4], leucocytosis [3], elevated ESR [2–5] or normocytic normochromic anaemia [4]. Muscle enzymes are usually within normal limits, although, in some cases, creatine kinase and aldolase are slightly elevated [3]. Electromyography is normal or shows a myopathic pattern in the affected muscle group [3, 5]. Plain X-ray reveals soft-tissue swelling and occasional periostitis [1, 5] in adjacent bones, leading to the suspicion of osteomyelitis or neoplasm. MRI shows a hypointense signal on T1-weighted sequences and a hyperintense signal on T2 and STIR sequences [5]. The diagnosis is based on the pathological findings, consisting of small and medium-sized muscle artery inflammation, with infiltration of vessel wall by neutrophils, lymphocytes, eosinophils and plasma cells, and fibrinoid necrosis. PAN confined to muscle can be misdiagnosed as focal nodular myositis [1, 3] because the clinical pictures of the two entities are very similar, and they share pathological findings such as endomysial and perimysial infiltration by mononuclear cells. The key point is the absence of true vasculitis in nodular myositis [6].

No case of PAN localized in muscle has been reported to evolve into systemic disease. The disease responds promptly to systemic glucocorticoids. Even treatment with indomethacin can occasionally control the disease [3]. Our case is the first description of spontaneous recovery in this process, giving rise to the hypothesis that necrotizing arteritis localized to muscle can run a milder course when associated with another connective tissue disease.

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Chondrodysplasic Rheumatism

Sir—The letter by Byrne and Rajan [1] published in this journal deserves the following remarks.

With my group, as early as 1970 [2, 3], I described arthropathies in (spondylo)-epiphyseal dysplasias under the appellation: chondrodysplasic rheumatism. This description, published in French, attracted the attention of E. G. L. Bywaters. He suggested that I should present our cases at the November 1973 session of the Heberden Society in which I was elected as a member [4]. Later on, with Professor S. de Seze, I wrote the chapter on heritable disorders of connective tissue disease in the first issue of Clinics in Rheumatic Diseases [5].

Like Byrne and Rajan, we have been impressed by the difficult differential diagnosis between cases of chronic juvenile arthritis and juvenile cases of chondrodysplasias.

Recent research in molecular biology carried out on collagen molecules may bring some light to the mechanism of premature generalized osteoarthritis. In our papers, we insisted on the fact that early lesions of the two entities are very similar, and they share pathological findings such as endomysial and perimysial infiltration by mononuclear cells. The key point is the absence of true vasculitis in nodular myositis [6].

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